

WHAT IS CLAIMED IS:

- 1           1. A method for screening a library of monomer domains or multimers  
2 comprising monomer domains for binding affinity to multiple ligands, the method comprising  
3                 contacting a library of monomer domains or multimers of monomer domains  
4 to multiple ligands; and  
5                 selecting monomer domains or multimers that bind to at least one of the  
6 ligands.
  
- 1           2. The method of claim 1, comprising  
2                 i. contacting a library of monomer domains to multiple ligands;  
3                 ii. selecting monomer domains that bind to at least one of the ligands;  
4                 iii. linking the selected monomer domains to a library of monomer  
5 domains to form a library of multimers, each comprising a selected monomer domain and a  
6 second monomer domain;  
7                 iv. contacting the library of multimers to the multiple ligands to form a  
8 plurality of complexes, each complex comprising a multimer and a ligand; and  
9                 v. selecting at least one complex.
  
- 1           3. The method of claim 2, the method further comprising  
2                 linking the multimers of the selected complexes to a library of monomer  
3 domains or multimers to form a second library of multimers, each comprising a selected  
4 multimer and at least a third monomer domain;  
5                 contacting the second library of multimers to the multiple ligands to form a  
6 plurality of second complexes; and  
7                 selecting at least one second complex.
  
- 1           4. The method of claim 2, wherein the identity of the ligand and the  
2 multimer is determined.
  
- 1           5. The method of claim 1, wherein a library of monomer domains is  
2 contacted to multiple ligands.
  
- 1           6. The method of claim 1, wherein a library of multimers is contacted to  
2 multiple ligands.

1                   7.     The method of claim 1, wherein the multiple ligands are in a mixture.  
1                   8.     The method of claim 1, wherein the multiple ligands are in an array.  
1                   9.     The method of claim 1, wherein the multiple ligands are in or on a cell  
2 or tissue.

1                   10.    The method of claim 1, wherein the multiple ligands are immobilized  
2 on a solid support.

1                   11.    The method of claim 1, wherein the ligands are polypeptides.  
1                   12.    The method of claim 12, wherein the polypeptides are expressed on the  
2 surface of phage.

1                   13.    The method of claim 1, wherein the monomer domain or multimer  
2 library is expressed on the surface of phage.

1                   14.    The method of claim 1, wherein the monomer domain is a LDL  
2 receptor type A monomer domain.

1                   15.    The method of claim 1, wherein the monomer domain is an EGF  
2 monomer domain.

1                   16.    The method of claim 1, wherein the library of multimers is expressed  
2 on the surface of phage to form library-expressing phage and the ligands are expressed on the  
3 surface of phage to form ligand-expressing phage, and the method comprises

4                   contacting library-expressing phage to the ligand-expressing phage to form  
5 ligand-expressing phage/library-expressing phage pairs;

6                   removing ligand-expressing phage that do not bind to library-expressing or  
7 removing library-expressing phage that do not bind to ligand-expressing phage; and  
8                   selecting the ligand-expressing phage/library-expressing phage pairs.

1                   17.    The method of claim 16, further comprising isolating polynucleotides  
2 from the phage pairs and amplifying the polynucleotides to produce a polynucleotide hybrid  
3 comprising polynucleotides from the ligand-expressing phage and the library-expressing  
4 phage.

1                   18.     The method of claim 17, comprising isolating polynucleotide hybrids  
2 from a plurality of phage pairs, thereby forming a mixture of polynucleotide hybrids.

1                   19.     The method of claim 18, comprising  
2                   contacting the mixture of hybrid polynucleotides to a cDNA library under  
3 conditions to allow for polynucleotide hybridization, thereby hybridizing a hybrid  
4 polynucleotide to a cDNA in the cDNA library; and  
5                   determining the nucleotide sequence of the hybridized hybrid polynucleotide,  
6 thereby identifying a monomer domain that specifically binds to the polypeptide encoded by  
7 the cDNA.

1                   20.     The method of claim 1, wherein the monomer domain library is  
2 expressed on the surface of phage to form library-expressing phage and the ligands are  
3 expressed on the surface of phage to form ligand-expressing phage, and the selected  
4 complexes comprise a library-expressing phage bound to a ligand-expressing phage and the  
5 method comprises:

6                   dividing the selected monomer domains or multimers into a first and a second  
7 portion,

8                   linking the monomer domains or multimers of the first portion to a solid  
9 surface and contacting a phage-displayed ligand library to the monomer domains or  
10 multimers of the first portion to identify target ligand phage that binds to a monomer domain  
11 or multimer of the first portion;

12                  infecting phage displaying the monomer domains or multimers of the second  
13 portion into bacteria to express the phage; and

14                  contacting the target ligand phage to the expressed phage to form phage pairs  
15 comprised of a target ligand phage and a phage displaying a monomer domain or multimer.

1                   21.     The method of claim 20, further comprising isolating a polynucleotide  
2 from each phage of the phage pair, thereby identifying a multimer or monomer domain that  
3 binds to the ligand in the phage pair.

1                   22.     The method of claim 23, further comprising amplifying the  
2 polynucleotides to produce a polynucleotide hybrid comprising polynucleotides from the  
3 target ligand phage and the library phage.

1                   23. The method of claim 20, comprising isolating and amplifying  
2 polynucleotide hybrids from a plurality of phage pairs, thereby forming a mixture of  
3 polynucleotide hybrids.

1                   24. The method of claim 23, comprising  
2                   contacting the mixture of hybrid polynucleotides to a cDNA library under  
3 conditions to allow for hybridization, thereby hybridizing a hybrid polynucleotide to a cDNA  
4 in the cDNA library; and  
5                   determining the nucleotide sequence of the associated hybrid polynucleotide,  
6 thereby identifying a monomer domain that specifically binds to the ligand encoded by the  
7 cDNA associated cDNA.